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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/295,464	04/19/1999	CHRISTOPHER J. ONG	80135-0	7207

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	23

DATE MAILED: 06/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/295,464	Ong et al
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 17, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-6, 9, 12, 13, and 15-19* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *9, 12, 13, and 15* is/are allowed.

6) ☒ Claim(s) *1, 3-6, and 16-19* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Apr 19, 1999* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Amendments were received and entered as Paper Nos. 21 and 22 on 2/6/03 and 4/17/03, respectively.

Claims 1, 3-6, 9, 12, 13, and 15-19 remain pending and are under consideration in this Office Action.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **SEQ ID NOS:1-4 are disclosed at pages 25 (lines 19 and 22) and 26 (lines 11 and 12), however the Office has not received a Sequence Listing in either a computer readable form or a paper copy.**

Applicant must provide:

An initial computer readable form (CRF) copy of the "Sequence Listing".

An initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the originally filed declaration was unsigned, subsequently a preliminary amendment was filed on 4/19/99, then an executed oath was filed on 8/23/99. However, the executed oath did not indicate that the specification as amended on 8/23/99 had been "reviewed and understood" by the inventors.

Rejections Withdrawn

The rejection of claims 12 and 13 under 35 USC 102 is withdrawn in view of Applicant's amendments.

The rejection of claims 1, 3-6, 9, 12, 13, and 15-19 under 35 USC first paragraph is withdrawn, but is replaced by the following new ground of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 3-6, 16, and 17 are drawn to methods of screening for the integration of a DNA construct into a target gene having restricted expression in a mouse. These claims require that detection of a detectable indicator is indicative of integration of a DNA construct into a gene having restricted expression. Claim 18 is drawn to a method of producing mouse tissue or specialized cells comprising a detectable indicator associated with a target gene having restricted expression. Claim 19 is drawn to a method of producing a mouse comprising a detectable indicator associated with a target gene having restricted expression.

The specification defines "restricted expression" as "the restriction of a transcription control element (such as a promoter or enhancer) or the restriction of expression of a gene, such that the aforesaid function or expression occurs in a particular tissue or cell type in a eukaryotic organism. Thus a gene or transcription control element having "restricted expression" is a tissue or cell specific gene or control element."

The invention functions as follows. First a mouse ES cell is transformed with a first DNA construct encoding an indicator component operably linked to a tissue specific promoter of choice. The resulting cell or its descendants are then transformed by a second DNA construct encoding a second indicator component, wherein the second construct lacks any transcription control element, and wherein the second construct integrates into the genome of the cell. The cells can then be made to differentiate into cells or tissue in which the chosen tissue specific promoter is active. In cells in which the integration event occurs in a gene that is expressed in the same tissue in which the tissue specific promoter of the first construct is active, both indicator

components will be expressed yielding a detectable signal. This allows one to isolate genes or promoters having tissue specific or developmentally regulated expression, and to make transgenic animals with mutations in such genes.

However, the claims lack critical method steps because they do not necessarily lead to the claimed result. While the method steps will necessarily lead to the detection of genes that are expressed in the same cell type in which the chosen tissue specific promoter is active, these genes need not also be expressed in a tissue restricted manner as required by the claims. One of ordinary skill in the art appreciates that there is a wide variety of genes that are expressed in a tissue specific fashion, but there is also a wide variety of genes that are expressed in all tissues, i.e. so-called housekeeping genes. Housekeeping genes include those genes that must be expressed in order to maintain all cells, e.g. those that fulfill the basic functions of cell metabolism such as membrane biosynthesis and turnover, nucleic acid metabolism, energy metabolism, and protein metabolism. Such genes would include those encoding proteins required for glycolytic, citric acid cycle, electron transport, and oxidative phosphorylation enzymes, ribosomal RNAs and ribosomal proteins, RNA polymerases, DNA polymerases in dividing cells, fatty acid biosynthesis and degradation enzymes, proteins involved in shuttling various molecules to different cellular compartments, cytoskeletal proteins, and many others. The claims recite no steps which would distinguish insertion events into housekeeping genes from insertion events into tissue specific genes. So, one following the recited method steps would not necessarily arrive at the desired outcome of identifying target genes that have restricted expression in a mouse. As such, one

could not know without executing further, currently unrecited, method steps whether the second construct had integrated into a housekeeping gene or a tissue-specific gene. Claims 1, 2-5, 16, and 17 require that the detection of a detectable indicator must be indicative of integration into a tissue restricted gene. However, the specification does not teach how to obtain this result without conducting basic research to first show that any identified gene was not actually a housekeeping gene. Therefore the specification fails to teach how to obtain a required objective, a detectable indicator which is indicative of integration into a gene having tissue-restricted expression, using the recited method steps. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the failure to teach how to obtain the required objective by following the recited method steps results in a failure to meet the enablement requirement.

Conclusion

Claims 9, 12, 13 and 15 are allowable. Claims 1, 3-6, and 16-19 are free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.